REMARKS

Rejections under 35 U.S.C. §112, second paragraph

Claims 17-19 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. More specifically, claim 17 has been rejected for lacking antecedent basis for "the HIV-1 Nef protein" and "targeted." Claim 17 has been amended to address this issue. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102(b)/103

Claims 1-4 have been rejected under 35 U.S.C. §102(b)/103 as being anticipated by or obvious over Lee et al. In response to Applicant's arguments, the Examiner asserts the following points.

1) The Examiner asserts that the disclosure of Lee et al. is not limited to one mutant, i.e. the Fyn SH3, SH3 domain. The Examiner asserts that Lee et al. teach making multiple SH3 kinase domains containing multiple mutant RT-loop w/n non-conserved regions.

2) The Examiner asserts that replacing the RT loop of the SH3 domain in Lee et al. with another known RT loop results in a non-wild-type SH3 domain and therefore a "new sequence."

3) The Examiner further maintains the position that Lee et al. teach the making of artificial SH3 domains through random substitutions. The Examiner relies on the Examples and Abstract of the reference for this point.

The Examiner further finds the Declaration of Dr. Saksela to be unpersuasive on the basis that a) the comments in the Declaration rely on features not recited in the claims and b) Dr. Saksela has not considered the entire teachings of the reference.

The Examiner maintains the rejection on the basis that the term "artificial SH3 domain" means any domain not present in nature; "randomized RT loops" means a wild-type RT loop containing one more amino acid substitutions; and "recombinant library" means a collection of at least two members produced recombinantly.

Finally, the Examiner asserts that Applicant's argument that Lee et al. fails to teach the creation of randomized libraries via site directed mutagenesis is not commensurate with the claims.

Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Claim 1 has been amended to be drawn to a method for generating artificial SH3 domains having ligand binding affinity that is higher than the affinity of corresponding wild-type SH3 domain which comprises:

a) producing a collection of DNA fragments encoding SH3 domains containing a randomized mutations in RT-loop (RRT-SH3 domains),

b) generating recombinant libraries comprising said RRT-SH3 domains,

c) subjecting said libraries to affinity or functional selection steps to identify artificial SH3 domains, and

d) selecting domains with an binding affinity that is higher than the binding affinity of the corresponding wild-type SH3 domain.

Thus, with the present invention, the method is specifically designed to generate and identify SH3 domains that have higher binding affinity than the corresponding wild-type domain. See for example, page 4, final sentence spanning page 5. There is no disclosure or suggestion in Lee et al. of obtaining SH3 domains having unnaturally high binding affinities.

The objectives of Lee et al. was to study the importance of the particular amino acid positions in the RT-loop with regard binding to Nef. See for example, the discussion on page 5009, that states,

> We then constructed and tested additional mutant Fyn SH3 domains to examine the individual contribution of each of the three Hck-specific amino acids (IHH) in providing Nef binding affinity for Fyn SH3 (See Table 1).

Thus, Lee et al. may be described as a domain mapping study, i.e. a study to determine the importance of particular amino acids in the Nef/kinase binding interaction. As noted in the Declaration of Dr. Saksela there was no objective in Lee et al. of creating and identifying "improved" RT-loop mutants. As a result, the approach taken in Lee et al. is to some extent the

opposite to the approach used with the invention. In Lee et al., a particular amino acid was deliberately replaced with a known amino acid residue, i.e. the identity of the amino acid being replaced and the identity of the new amino acid were known prior to the modification, with the impact on binding being subsequently studied. In the present, the mutations made are unknown and not determined until subsequent to the determination on the impact on binding. This feature is reflected in the recitation of "randomized RT-loop". There is no disclosure in Lee et al. or using randomized mutations. In addition, being a domain mapping study there is no disclosure or suggestion in Lee al. of creating and identifying artificial SH3 domains having improved binding properties compared to the wild-type domain. As such, the present invention is not anticipated by Lee et al. and withdrawal of the rejection is respectfully requested.

Claims 1-4 and 17-19 have been rejected under 35 U.S.C. §103 as being obvious over Lee et al. combined with Sparks et al. The Examiner finds Applicant's previous argument insufficient to overcome the rejection for the following reasons.

1) The Examiner asserts that Applicants improperly attacked the Sparks reference individually.

2) The Examiner asserts that motivation to combine the references is found in both the reference teachings and the generally available knowledge in the art. Specifically, the

Examiner asserts that Lee et al. teaches making recombinant libraries by the randomization of the non-conserved RT-loop hexapeptide of Hck or of the equivalent region of other proteins of the Src family. The Examiner further asserts that "one would be motivated to completely randomize the hexapeptide variable RT loop region in order to obtain the largest possible library...thus *optimizing* the likelihood of finding therapeutically useful competitive inhibitors."

As stated above, Lee et al. fails to teach a method for generating SH3 domains having higher than natural binding affinity. Sparks et al. similarly fails to teach the generation of proteins having higher than natural binding properties. Although random peptide libraries were used in Sparks et al., the problem being addressed in the reference was similar to that in Lee et al., i.e. Sparks et al., like Lee et al., is a "domain mapping study", i.e. a study to determine which amino acids are involved with and important for ligand binding. There is no suggestion in Sparks et al. of obtaining super-binding proteins.

As such, the invention cannot be achieved when Lee et al. and Sparks et al. are combined. Applicants have not attacked the references individually. Applicants have pointed out that both references have the same deficiency therefore the invention cannot be achieved by combining the references. As such, the invention is not obvious over the references and withdrawal of the rejection is respectfully requested.

Should the Examiner have any questions regarding the present application she is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

Applicants request of two (2) month extension of time for filing the present response. The required fee is attached hereto.

A marked-up version of claims 1 and 17 showing all changes is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/MAA/

Attachment: Marked-up Version Showing Changes

MARKED-UP VERSION SHOWING CHANGES

IN THE CLAIMS

Claims 1 and 17 have been amended as follows.

1. (Thrice amended) A method for generating artificial SH3 domains having ~~desired~~ ligand binding **affinity that is higher than the affinity of corresponding wild-type SH3 domain** ~~properties and screening the domains for desired ligand binding properties,~~ which comprises:

a) producing a collection of DNA fragments encoding SH3 domains containing a randomized **mutations in** RT-loop (RRT-SH3 domains),

b) generating recombinant libraries comprising said RRT-SH3 domains, ~~and~~

c) subjecting said libraries to affinity or functional selection steps to identify artificial SH3 domains**, and**

d) selecting domains with a binding affinity that is higher than the binding affinity of the corresponding wild-type SH3 domain.

17. (Twice Amended) The method according to claim 3, wherein the six amino acids that are replaced in the RT-loop are replaced with a peptide motif derived from Hck-SH3 and **which binds to** ~~targeted to the~~ HIV-1 Nef protein selected from the group

consisting of XSWSXX (SEQ ID NO:28), XSPFXX (SEQ ID NO:30) and XSXFPW (SEQ ID NO:32), wherein X is any amino acid.